Dynamics of Multiple Pathogen Strains in Heterosexual Epidemiological Models

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DYNAMICS OF MULTIPLE PATHOGEN STRAINS IN HETEROSEXUAL EPIDEMIOLOGICAL MODELS

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ABSTRACT

A heterosexually active population is exposed to n competing strains or n distinct sexually-transmitted pathogens. It is assumed that a host cannot be invaded simultaneously by more than one disease agents and that when symptoms appear, a function of the pathogen or strain virulence, individuals recover. We conclude that in a behaviorally and genetically homogeneous population coexistence is not possible except under very special circumstances. The mathematical qualitative analysis of our model is complete. That is, a global stability analysis of the stationary states is provided.

1. Introduction

Molecular studies have shown poplymorphism in viral populations quite common. For example, there are various gonococci strains existing in human populations, some of which are resistant to all forms of penicillin while most strains can be treated by penicillin (e.g. see Hethcote and Yorke[13]). Biologists have also long been concerned with the evolutionary interactions that result from changing host and pathogen populations (Ewald[12]). A growing number of studies in human and animal behavior have brought to the forefront of research the importance of group and individual behavior on the evolution of disease. Social and disease dynamics do not operate in independent environments. In fact, their effects are closely linked ().

Host-vector interactions such as those observed in the myxoma-rabbit system challenge standard views of pathogen evolution while providing a fertile ground for the study of coevolutionary interactions. If one sees hosts as patches that may be colonized by infectious pathogens the following questions arise: What are the possible outcomes of coevolutionary races where different strains of the same pathogen compete for the same patches/resource? What conditions are needed for a competitive exclusion? What happens if patches change; that is, what happens if a new breed of resistant patches develop? Mathematical models and systematic field

studies have begun to yield useful new paradigms for the study of coevolutionary interactions (Anderson and May[1,2], Beck[3], Bremermann and Pickering[4], Bremermann and Thième[5], Castillo-Chavez et al.[6,7], Dietz[10] Dwyer et al.[11], Fenner and Myers[13], Fenner and Ratcliffe[14], Levin[16,17], Levin and Pimentel[18], May and Anderson19). Castillo-Chavez et al.[8] formulated a simple two-sex epidemiological model with two pathogen strains. They found out that coexistence of two competing strains is not possible regardless of initial conditions except in special and unrealistic circumstances, which is similar to the results obtained by Bremerman and Thieme[5] for SIR models with variable population size, but only one gender of the host.

In this manuscript, we extend the two-sex model studied in Castillo-Chavez et al.[8] to including n pathogen strains. A complete mathematical analysis for the global behavior of the infection-free equilibrium and all other endemic equilibria is provided. The biological outcome is similar to that in Castillo-Chavez et al.[8] However, since the type K monotonicity no longer works for the case with n pathogen strains, different approaches, based on the comparison principle, are employed.

This manuscript is organized as follows: Section 2 introduces our model and simplifies it using some recent results on asymptotically autonomous epidemic models (Thieme[20], Castillo-Chavez and Thieme[9]); in Section 3, we compute the necessary thresholds and study the stability of the infection-free state; a principle of competitive exclusion for SIS models with homogeneous mixing is established in Section 4 through the existence, uniqueness of endemic equilibria and their stability.

2. Model Description

Consider a two-sex S-I-S sexually transmitted disease (STD) model in a heterosexual population with n pathogen strains in the infected subpopulations. superscripts m and f are used to denote male and female respectively. We assume that the infecteds are divided into n groups based on the pathogen strains that they carry and that susceptibles infected by infecteds with a certain strain will have the same strain. Then the dynamics of the spread of the disease are governed by

$$\begin{cases} \dot{S}^m = \Lambda^m - B^m - \mu S^m + \sum_{i=1}^{n} \gamma_i^m I_i^m, \\ \dot{I}_i^m = B_i^m - (\mu + \gamma_i^m) I_i^m, \\ \dot{S}^f = \Lambda^f - B^f - \mu S^f + \sum_{i=1}^{n} \gamma_i^f I_i^f, \\ \dot{I}_i^f = B_i^f - \left(\mu + \gamma_i^f\right) I_i^f, \end{cases} \tag{2.1}$$

where

$$B_i^m = r^m\left(T^m, T^f\right) S^m \beta_i^f \frac{I_i^f}{T^f}, \qquad B_i^f = r^f\left(T^m, T^f\right) S^f \beta_i^m \frac{I_i^m}{T^m},$$

$$B^m = \frac{r^m\left(T^m, T^f\right) S^m}{T^f} \sum_{j=1}^{n} \beta_j^f I_j^f, \qquad B^f = \frac{r^f\left(T^m, T^f\right) S^f}{T^m} \sum_{j=1}^{n} \beta_j^m I_j^m.$$

Here Λ^k, $k = m, f$ denote the "recruitment" rates into the sexually active populations; μ^k are the natural death rates for males and females respectively (which includes retirement from sexual activity); γ_i^k denote the rates of recovery (this includes the time that it takes to become symptomatic); β_i^k denote the transmission rates of infection; T^m and T^f are the total number of males and females respectively; and r^k, as functions of T^m and T^f, give the average rates of partner acquisition per male and per female and satisfy the constraint

$$r^m\left(T^m, T^f\right) T^m = r^f\left(T^m, T^f\right) T^f, \tag{2.2}$$

which indicates that the total average contact rate of females equals the total average contact rate of males.

Since $T^k = S^k + \sum_{i=1}^{n} I_i^k$, (2.1) is equivalent to

$$\begin{cases} \dot{T}^m = \Lambda^m - \mu^m T^m, \\ \dot{T}^f = \Lambda^f - \mu^f T^f, \\ \dot{I}_i^m = -\left(\mu^m + \gamma_i^m\right) I_i^m + r^m\left(T^m, T^f\right) \beta_i^f \dfrac{\left(T^m - \sum\limits_{j=1}^{n} I_j^m\right) I_i^f}{T^f}, \\ \dot{I}_i^f = -\left(\mu^f + \gamma_i^f\right) I_i^f + r^f\left(T^m, T^f\right) \beta_i^m \dfrac{\left(T^f - \sum\limits_{j=1}^{n} I_j^f\right) I_i^m}{T^m}. \end{cases} \tag{2.3}$$

The equilibrium for T^k is

$$T^m = \frac{\Lambda^m}{\mu^m}, \qquad T^f = \frac{\Lambda^f}{\mu^f}.$$

Define

$$c^m := r^m\left(\Lambda^m/\mu^m, \Lambda^f/\mu^f\right), \qquad c^f := r^f\left(\Lambda^m/\mu^m, \Lambda^f/\mu^f\right).$$

Then it follows from the constraint (2.2) that $c^m \Lambda^m = c^f \Lambda^f$, as $t \to \infty$.

The limiting system of (2.3) is

$$\begin{cases} \dot{I}_i^m = -\left(\mu^m + \gamma_i^m\right) I_i^m + \dfrac{\mu^f c^m \beta_i^f}{\Lambda^f}\left(\dfrac{\Lambda^m}{\mu^m} - \sum\limits_{j=1}^{n} I_j^m\right) I_i^f, \\ \dot{I}_i^f = -\left(\mu^f + \gamma_i^f\right) I_i^f + \dfrac{\mu^m c^f \beta_i^m}{\Lambda^m}\left(\dfrac{\Lambda^f}{\mu^f} - \sum\limits_{j=1}^{n} I_j^f\right) I_i^m. \end{cases} \tag{2.4}$$

Set $\sigma_i^k := \left(\mu^k + \gamma_i^k\right)$, $a_i^m := \dfrac{\mu^f c^m \beta_i^f}{\Lambda^f}$, $a_i^f := \dfrac{\mu^m c^f \beta_i^m}{\Lambda^m}$, and $p^k := \dfrac{\Lambda^k}{\mu^k}$. System (2.4) can be rewritten as

$$\begin{cases} \dot{I}_i^m = -\sigma_i^m I_i^m + a_i^m\left(p^m - \sum\limits_{j=1}^{n} I_j^m\right) I_i^f, \\ \dot{I}_i^f = -\sigma_i^f I_i^f + a_i^f\left(p^f - \sum\limits_{j=1}^{n} I_j^f\right) I_i^m. \end{cases} \tag{2.5}$$

The dynamics of (2.1) or (2.3) can be qualitatively determined by those of (2.5) (e.g. see Castillo-Chavez et al.[8] and Castillo-Chavez and Thieme[9]). We will investigate (2.5) hereafter.

3. Thresholds

The threshold conditions are determined by the stability of the infection-free equilibrium and are characterized by the so-called reproductive number. We derive the reproductive number for each pathogen strain as follows.

The linearization about the infection-free equilibrium is

$$\begin{cases} \dot{I}_i^m = -\sigma_i^m I_i^m + a_i^m p^m I_i^f, \\ \dot{I}_i^f = -\sigma_i^f I_i^f + a_i^f p^f I_i^m, \end{cases} \qquad i = 1, \cdots, n. \tag{3.1}$$

Equations in (3.1) are n decoupled systems of two equations. If

$$\sigma_i^m \sigma_i^f > a_i^m a_i^f p^m p^f, \qquad i = 1, \cdots, n,$$

the infection-free equilibrium is table. If there exists $1 \le i \le n$ such that

$$\sigma_i^m \sigma_i^f < a_i^m a_i^f p^m p^f,$$

the infection-free equilibrium is unstable.

We define the reproductive number in the ith subgroup by

$$R_i := \frac{c^m c^f \beta_i^m \beta_i^f}{(\mu + \gamma_i^m)\left(\mu + \gamma_i^f\right)}. \tag{3.2}$$

Then if $R_i \le 1$, $\left(I_i^m, I_i^f\right) \to (0,0)$. If $R_i \le 1$, for all i, the infection-free equilibrium is stable which leads to the extinction of the disease in the population. However, if there exists at least one subgroup such that $R_i > 1$, then $\left(I_i^m, I_i^f\right) \not\to (0,0)$, which leads to the spread of the disease in the population. Moreover, if $R_i \le 1$, the infection-free equilibrium is globally stable. Before a detailed proof is given, we state the following lemma which is needed for the proof here as well as that in Section 4.

Lemma 3.1. (Theorem 4.1.2 in Castillo-Chavez et al.[8]) *Consider the following system of differential equations:*

$$\begin{cases} \dot{\widehat{I}}_i^m = -\sigma_i^m \widehat{I}_i^m + a_i^m \left(p^m - \sum_{j=1}^{2} \widehat{I}_j^m\right) \widehat{I}_i^f, \\ \dot{\widehat{I}}_i^f = -\sigma_i^f \widehat{I}_i^f + a_i^f \left(p^f - \sum_{j=1}^{2} \widehat{I}_j^f\right) \widehat{I}_i^m, \end{cases} \qquad i = 1, 2.$$

Let

$$\widehat{R}_i := \frac{a_i^m a_i^f p^m p^f}{\sigma_i^m \sigma_i^f}, \qquad i = 1, 2.$$

Then, if $\widehat{R}_i \le 1$, $\lim_{t\to\infty} \widehat{I}_i^k(t) = 0$, *for all* $I_i^k(0) > 0$, $i = 1, 2$, $k = m, f$. *If* $\widehat{R}_j > \widehat{R}_l > 1$, $j, l = 1, 2$, $j \ne l$, *then* $\lim_{t\to\infty} \widehat{I}_l^k(t) = 0$, *for all* $I_l^k(0) > 0$, $k = m, f$.

We now turn to the proof of the global stability of the infection-free equilibrium if $R_i \le 1$ for all i.

For any $1 \le j, l \le n$, $j \ne l$, we consider

$$\begin{cases} \dot{\widehat{I}}_j^m = -\sigma_j^m \widehat{I}_j^m + a_j^m \left(p^m - \left(\widehat{I}_j^m + \widehat{I}_l^m\right)\right) \widehat{I}_j^f, \\ \dot{\widehat{I}}_j^f = -\sigma_j^f \widehat{I}_j^f + a_j^f \left(p^f - \left(\widehat{I}_j^f + \widehat{I}_l^f\right)\right) \widehat{I}_j^m, \\ \dot{\widehat{I}}_l^m = -\sigma_l^m \widehat{I}_l^m + a_l^m \left(p^m - \left(\widehat{I}_j^m + \widehat{I}_l^m\right)\right) \widehat{I}_l^f, \\ \dot{\widehat{I}}_l^f = -\sigma_l^f \widehat{I}_l^f + a_l^f \left(p^f - \left(\widehat{I}_j^f + \widehat{I}_l^f\right)\right) \widehat{I}_l^m. \end{cases}$$

Let $\widehat{R}_j$ and $\widehat{R}_l$ be the reproductive numbers for group j and group l respectively. Then, $\widehat{R}_j = R_j$ and $\widehat{R}_l = R_l$. Since $R_i \le 1$ for all i, which implies $\widehat{R}_j \le 1$ and $\widehat{R}_l \le 1$, it follows from Lemma 3.1 that $\lim_{t\to\infty} \widehat{I}_j^k(t) \to 0$ and $\lim_{t\to\infty} \widehat{I}_l^k(t) \to 0$, as $t \to \infty$, for all $\widehat{I}_j^k(0) > 0$ and $\widehat{I}_l^k(0) > 0$, $k = m, f$. On the other hand, from the comparison principle, it follows that $I_j^k(t) \le \widehat{I}_j^k(t)$, $I_l^k(t) \le \widehat{I}_l^k(t)$, $k = m, f$, for all $t \ge 0$. Thus, the infection-free equilibrium is globally stable. In summary, we have

Theorem 3.2. *Let the reproductive number* R_i *for each group be defined in* (3.2). *Then, if* $R_i \le 1$, *for all* $1 \le i \le n$, *the epidemic goes extinct regardless of the initial levels of infection. If* $R_i > 1$ *for some* $1 \le i \le n$, *then the epidemic spreads in the population.*

4. Endemic equilibria

It is similar to the cases discussed in Castillo-Chavez et al.[8] that there exist two types of endemic equilibria, one of which consists of one nonzero pair (I_i^m, I_i^f) and the other pair being zero, and one of which consists of more than one nonzero pairs. The qualitative behavior of these equilibria are determined by the reproductive numbers for the subgroups. We refer the formal as "winner equilibria" and the latter as "coexistence equilibria" (Castillo-Chavez et al.[8]). The dynamics of the winner equilibria are investigated as follows.

Theorem 4.1. *Assume that* $R_i > 1$, $1 \le i \le n$. *Then the nontrivial equilibrium* $(S^k > 0, I_i^k > 0, I_j^k = 0, j \ne i)$ *exists.*

Proof. We need to solve

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - \sum_{l\in\Omega} I_l^m\right) I_i^f, \\ \sigma_i^f I_i^f = a_i^f \left(p^f - \sum_{l\in\Omega} I_l^f\right) I_i^m, \end{cases}$$

for I_i^k, $0 < I_i^k < p^k$.

A straightforward algebraic manipulation leads to

$$I_i^m = \frac{a_i^m a_i^f p^m p^f - \sigma_i^m \sigma_i^f}{a_i^f \left(\sigma_i^m + a_i^m p^f\right)} = \frac{(R_i - 1)\sigma_i^m \sigma_i^f}{a_i^f \left(\sigma_i^m + a_i^m p^f\right)},$$
$$I_i^f = \frac{a_i^m a_i^f p^m p^f - \sigma_i^m \sigma_i^f}{a_i^m \left(\sigma_i^f + a_i^f p^m\right)} = \frac{(R_i - 1)\sigma_i^m \sigma_i^f}{a_i^m \left(\sigma_i^f + a_i^f p^m\right)}.$$

$I_i^k > 0$ if and only if $R_i > 1$. The proof is complete.

Among these winner equilibria, there exists only one which is globally stable and the others are unstable. The stability is completely determined the reproductive numbers. Based on Lemma 3.1, we have

Theorem 4.2. *Let there be more than one reproductive numbers greater than one and assume that they are distinct. If R_i is the largest among those reproductive numbers, then the nontrivial equilibrium $\left(S^k > 0, I_i^k > 0, I_j^k = 0, j \neq i, k = m, f\right)$ is stable and the other equilibria $\left(S^k > 0, I_j^k > 0, I_l^k = 0, l \neq j, k = m, f\right)$, $j \neq i$, are unstable.*

Proof Without loss of generality, we assume $R_1 > R_j$, for all $j \neq 1$. For any $j > 1$, consider

$$\begin{cases} \dot{\widehat{I}}_1^m = -\sigma_1^m \widehat{I}_1^m + a_1^m \left(p^m - \left(\widehat{I}_1^m + \widehat{I}_j^m\right)\right) \widehat{I}_1^f, \\ \dot{\widehat{I}}_1^f = -\sigma_1^f \widehat{I}_1^f + a_1^f \left(p^f - \left(\widehat{I}_1^f + \widehat{I}_j^f\right)\right) \widehat{I}_1^m, \\ \dot{\widehat{I}}_j^m = -\sigma_j^m \widehat{I}_j^m + a_j^m \left(p^m - \left(\widehat{I}_1^m + \widehat{I}_j^m\right)\right) \widehat{I}_j^f, \\ \dot{\widehat{I}}_j^f = -\sigma_j^f \widehat{I}_j^f + a_j^f \left(p^f - \left(\widehat{I}_1^f + \widehat{I}_j^f\right)\right) \widehat{I}_j^m. \end{cases}$$

Let $\widehat{R}_1$ and $\widehat{R}_j$ be the reproductive numbers for group 1 and group j respectively. Then, $\widehat{R}_1 = R_1$ and $\widehat{R}_j = R_j$. Hence $\widehat{R}_1 > \widehat{R}_j$ and it follows from Lemma 3.1 that $\lim_{t\to\infty} \widehat{I}_j^k(t) = 0$, for all $\widehat{I}_j^k(0) > 0$, $k = m, f$. Again, from the comparison principle, $I_j^k(t) \leq \widehat{I}_j^k(t)$, $k = m, f$, for all $t \geq 0$. Hence, $\lim_{t\to\infty} I_j^k(t) = 0$, $k = m, f$. Since j is arbitrary, all solution trajectories approach the equilibrium $\left(S^k > 0, I_1^k > 0, I_j^k = 0, j \neq 1, k = m, f\right)$. The conclusion follows.

Coexistence of more than one different pathogen strains, i.e. existence of the coexistence equilibria, occurs only if these pathogen strains have the same reproductive number as can be seen in the following.

Theorem 4.3. *Let Ω be a nonempty subset of $\{1, 2, \cdots, n\}$. Then there exists a nontrivial equilibrium $\left(S^k > 0, I_l^k > 0, l \in \Omega, I_u^k = 0, u \notin \Omega\right)$ if*

$$R_i = R_j, \qquad \forall i, j \in \Omega.$$

Proof. Suppose that such a nontrivial equilibrium exists. Then

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - \sum\limits_{l\in\Omega} I_l^m\right) I_i^f, \\ \sigma_i^f I_i^f = a_i^f \left(p^f - \sum\limits_{l\in\Omega} I_l^f\right) I_i^m, \end{cases}$$

that is,

$$\begin{cases} I_i^m = \dfrac{a_i^m}{\sigma_i^m}\left(p^m - \sum\limits_{l\in\Omega} I_l^m\right) I_i^f, \\ I_i^f = \dfrac{a_i^f}{\sigma_i^f}\left(p^f - \sum\limits_{l\in\Omega} I_l^m\right) I_i^m. \end{cases}$$

Hence

$$\frac{a_i^m a_i^f}{\sigma_i^m \sigma_i^f}\left(p^m - \sum_{l\in\Omega} I_l^m\right)\left(p^f - \sum_{l\in\Omega} I_l^f\right) = 1,$$

or

$$\frac{\mu^2}{\Lambda^m \Lambda^f}\left(p^m - \sum_{l\in\Omega} I_l^m\right)\left(p^f - \sum_{l\in\Omega} I_l^f\right)\frac{c^m c^f \beta_i^m \beta_i^f}{\left(\mu+\gamma_i^m\right)\left(\mu+\gamma_i^f\right)} = 1,$$

which holds for all $i \in \Omega$. This completes the proof.

Now we assume that there exist q subgroups which have the same reproductive number, $R_i = R_j$, $1 \le i,j \le q$. Then we can explicitly solve for a continuum of coexistence equilibria; that is, $I_i^k > 0$ for all $1 \le i \le q$.

Theorem 4.4. *Assume that there are q subgroups such that $R_i = R$ for all $1 \le i \le q$. Then there exists a q-dimensional continuum of equilibria*

$$\begin{cases} I_i^m = \dfrac{p^m\left(R\sigma_l^m + p^f a_l^m\right) a_i^m \alpha_i}{R\sigma_i^m\left(p^f a_l^m + \sigma_l^m\left(1 - \sum\limits_{j\in U}\left(a_l^m/\sigma_l^m - a_j^m/\sigma_j^m\right)\right)\alpha_j\right)}, & i \in U, \\ I_i^f = \alpha_i, & i \in U, \\ I_l^m = \dfrac{p^m a_l^m\left(p^f\sigma_l^m(R-1) - \sigma_l^m \sum\limits_{j\in U}\left(R + p^f a_j^m/\sigma_j^m\right)\alpha_j\right)}{R\sigma_i^m\left(p^f a_l^m + \sigma_l^m\left(1 - \sum\limits_{j\in U}\left(a_l^m/\sigma_l^m - a_j^m/\sigma_j^m\right)\right)\alpha_j\right)}, & l \notin U \\ I_l^f = \dfrac{p^f\sigma_l^m(R-1) - \sigma_l^m \sum\limits_{j\in U}\left(R + p^f a_j^m/\sigma_j^m\right)\alpha_j}{R\sigma_l^m + p^f a_l^m}, \end{cases} \tag{4.1}$$

where $U := \{i_1, \cdots, i_{q-1}\} \subset \{1, \cdots, q\}$; $\alpha_i > 0$ are $q-1$ arbitrary constants satisfying

$$\sum_{j\in U}\left(R + p^f\frac{a_j^m}{\sigma_j^m}\right)\alpha_j < p^f(R-1). \tag{4.2}$$

Proof We need to solve the following system

$$\begin{cases} \sigma_i^m I_i^m = a_i^m \left(p^m - \sum_{j=1}^{q} I_j^m \right) I_i^f, \\ \sigma_i^f I_i^f = a_i^f \left(p^f - \sum_{j=1}^{q} I_j^f \right) I_i^m, \end{cases} \tag{4.3}$$

for $I_i^k > 0$ with $\sum_{j=1}^{q} I_j^m < p^m$ and $\sum_{j=1}^{q} I_j^f < p^f$.

¿From (4.3), we can solve for I_i^m such that

$$I_i^m = \frac{p^m a_i^m I_i^f}{\sigma_i^m \left(1 + \sum_{j=1}^{q} \frac{a_j^m}{\sigma_j^m} I_j^f \right)}. \tag{4.4}$$

Substitute (4.4) into $(4.3)_2$. Then a straightforward algebraic manipulation gives

$$\sum_{j}^{q} \left(R + p^f \frac{a_j^m}{\sigma_j^m} \right) I_j^f = p^f (R - 1).$$

Choosing q−1 $I_j^f = \alpha_j > 0$ satisfying (4.2), we obtain I_l^f as in $(4.1)_4$. Then $(4.1)_1$ and $(4.1)_3$ follow from (4.4).

It is not difficult to see that this continuum is stable. Because of less biological interest, the details are omitted.

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